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BY EMINENT AUTHORITIES IN GREAT BRITAIN, THE UNITED STATES AND THE CONTINENT

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VOLUME III

INFECTIOUS DISEASES (CONTINUED)—DISEASES OF THE RESPIRATORY TRACT

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PART I.

THE INFECTIOUS DISEASES—CONTINUED.

CHAPTER I.

MALTA FEVER.

By COL. DAVID BRUCE, C. B., F. R. S., D. Sc.

Synonym.—Mediterranean fever.

Definition.—A disease of long duration, characterized clinically by continued fever, profuse perspiration, constipation, frequent relapses, rheumatic or neuralgic pains, swelling of joints, or orchitis; bacteriologically, by the presence in the blood and organs of the *Micrococcus melitensis* (Bruce); and, anatomically, by congestion of the spleen and other organs.

History.—This fever has been elucidated chiefly by army medical officers, and its history may be briefly summed up as follows: The first paper of any importance was written in 1861 by Marston.[1] In it he described the fever from the clinical side very completely and clearly; and it will repay anyone interested in the disease to read his account. The next is by Veale,[2] in 1879, in which he describes the fever in patients invalided to England from Gibraltar, Malta and Cyprus. The next event of any importance was the discovery on July 9, 1887, of the specific organism of the disease, the *Micrococcus melitensis*.[3] Ten years afterward, in 1897, Wright and Semple applied the method of serum diagnosis to this fever, and this, especially in Malta, has helped greatly to distinguish this disease from other continued fevers. In this year, also, the late Surgeon-Captain M. Louis Hughes[4] published his lengthy monograph on *Mediterranean, Malta or Undulant Fever*, which contains everything known on the subject up to that date and also a full bibliography. Nothing more was done in the investigation of this fever until 1904, when a commission was formed, under the direction of the Royal Society of London, to continue the investigation. This commission

[1] *Army Medical Report*, 1863, vol. iii, p. 486.
[2] *Army Medical Report*, 1881, vol. xxi, p. 260.
[3] "Note on the Discovery of a Microörganism in Malta Fever," by Surgeon-Captain D. Bruce, *Practitioner*, vol. xxxix, 1887; and "The Micrococcus of Malta Fever," *Practitioner*, vol. xl, 1888; and "On the Etiology of Malta Fever," *Army Medical Report*, 1892, vol. xxxii, p. 365.
[4] *Mediterranean, Malta or Undulant Fever*, MacMillan & Co., 1897.

has been at work up to the present year (1907), and has furnished seven volumes of reports.[1]

Geographical Distribution.—This fever has been reported from *Spain*—Gibraltar; *Islands of the Mediterranean*—Balearic Islands, Corsica, Sardinia, Sicily, Malta, Gozo, Cyprus, Crete; *Italy*; *Greece*—Athens; *Turkey*—Constantinople, Smyrna; *Palestine*—Jerusalem; *Africa*—Tunis, Algiers, Alexandria, Suakin, Massowah, Zanzibar, Kimberley, Orange River Colony; *Arabia*—Aden; *India*; *China*—Hong Kong; *Pacific*—Philippine Islands, Fiji Islands; *North America*—Mississippi Valley; *West Indies*—Cuba, Porto Rico; *South America*—Venezuela, Brazil, Montevideo.

It is probable that many of these reported cases were not really Malta fever. The diagnosis was often made by the serum reaction to *Micrococcus melitensis*, a method which when used alone is apt to cause error. That the disease is a widespread one there can be no question, but it does not appear to occur in large numbers in any place except Malta, which is the home of this fever. It may also be said to be tropical and subtropical in its distribution, no cases, according to Hughes, having been reported north of 45° N. latitude, or south of 40° S. latitude.

Distribution in Malta.—Malta fever was thought at one time to be chiefly confined to the large towns of Malta, but now it is known to occur in every part of the island, and the disease is very prevalent in several of the inland towns and villages. The average incidence of the fever among the 200,000 Maltese is said to be about 30 per 10,000; whilst among the soldiers quartered in the island the incidence is about 370 per 10,000. In some years the incidence is double this, as, for example, in 1905 there were 643 cases of Malta fever among the soldiers alone (750 per 10,000) of whom 382 were invalided to England.

Etiology.—The Micrococcus Melitensis.—This coccus, or coccobacillus, is about 0.33μ in diameter, and usually occurs singly or in pairs, but when grown in broth appears in short chains. A bacillary form also occurs in cultures which have been grown at ordinary temperatures (18° C. to 20° C.). It is non-motile. It stains readily with all the basic aniline dyes, but loses its color rapidly when treated with alcohol or other decolorizing agent, and becomes unstained by Gram's method.

Artificial Cultivation.—Growth is extremely slow, and it is important that media which are faintly acid should be used. If markedly alkaline no growth whatever takes place. It shows a very slow and scanty growth at a temperature of 18° C., growing best at about 37° C. or 38° C. At temperatures between 40° C., and 42° C. growth is suspended. Above 42° C. artificial growths die. It is aërobic, but also grows in a feeble way anaërobically. The chief cultural characteristics are as follows:

In 1 per cent. glucose peptone, there is growth, but neither acid nor gas is produced. The same want of reaction occurs with lactose, saccharose, and starch peptone.

In litmus milk there is no clotting, and the reaction becomes distinctly alkaline in a few weeks.

[1] *Reports of the Commission Appointed by the Admiralty, the War Office, and the Civil Government of Malta, for the Investigation of Mediterranean Fever, Under the Supervision of an Advisory Committee of The Royal Society*, Parts I, II, III, IV, V, VI and VII, London: Harrison & Sons, 1905–06–07.

On potato it grows well; the growth is moist, transparent, and the formation of chains is well marked.

Growth in Broth.—After two or three days the broth becomes turbid. If allowed to stand for some time there is a deposit of flocculi, but the fluid remains turbid, and there is no pellicle formation. Indol reaction is negative. No odor is produced.

Growth on Gelatine.—Does not liquefy.

Growth on Agar-agar.—Cultures made directly from the organs after death on this medium, if faintly alkaline, show no growth for about four days, if kept at 37° C., and seven days if kept at 25° C. On sloped agar the colonies when they do appear are small and transparent, and resemble drops of dew.

Plate Cultivation.—On ordinary agar at 37° C., after three days, under the microscope the colonies on the surface are round, with an even border. They are bright and transparent, with a slight brown tinge about the centre, and are finely granular. As they grow older they become browner in color.

The addition of 1 per cent. nutrose enhances and quickens the growth of the micrococcus. To separate it from a mixture of others, it is best to use a medium to which glucose, nutrose, and litmus are added. The fact that it does not ferment glucose, and renders milk and other media alkaline, is an important feature, while the addition of nutrose adds somewhat to its rate of growth. On such a glucose-nutrose-litmus agar, the colonies appear blue, whereas many of the streptococci found in urine, fæces, etc., ferment glucose and give the medium an acid reaction.

In regard to the diagnosis of this species of bacteria, Horrocks says that a microörganism which agglutinates with a specific animal serum in a high dilution, does not ferment glucose, renders milk alkaline without coagulation, and does not retain stain by Gram's method, may justly be regarded as the *Micrococcus melitensis*.

Life of the Micrococcus Melitensis Outside the Body.—*Vitality.*—It is fairly resistant when outside the body. The most important facts are that it will resist desiccation in dust or on dry fabrics for sixty to eighty days. It will live in tap- or sea-water for about a month. Even in urine which has become markedly alkaline it has been found alive after six days. Exposure to the sun kills it in a few hours.

Habitat Outside the Human Body.—No one has, up to the present, found this parasite in external nature. The writer wrote in 1887 that, on account of the high temperature required for its growth, the length of time which elapses before the colonies appear, and the absence of any well-marked morphological or cultural characteristics, the search for it outside the body will be very difficult, if not hopeless. Many efforts have been made to find it in the air of wards, in dust from infected rooms, in the water of the harbors, or in the soil. Examinations of these materials have been made by plate cultures and by inoculation into susceptible animals, but without result.

How Does The Micrococcus Leave the Body?—All examinations of expired air, sweat, saliva, and scrapings of skin of patients have failed to show that the organism leaves the body by any of these routes. The urine, on the other hand, frequently contains them, sometimes in enormous numbers, but, as a rule, they are not numerous, ranging from 3 or 4 to 300 or 400 per cubic centimeter. Kennedy, a member of the Mediterranean Fever Commission, reports that he made some three thousand observations on the urine and found the *Micrococcus melitensis* in 10 per cent. This, taken

in connection with the long-continued vitality and virulence of the organism in a dry condition, may be a factor in the spread of the disease, though it must be confessed that up to the present there is no direct proof of infection by naturally infected dust. This excretion in the urine may go on for a long time (two years) after the patient is convalescent, so that these microbes must be scattered broadcast over the whole of Malta. It has not yet been ascertained how many cases of Malta fever remain unidentified, but there can be little doubt that many do, and these add to the general contamination of the surface of the soil. Shaw[1] examined 525 dockyard laborers and found that 79, or 15 per cent., gave a distinct agglutination with the *Micrococcus melitensis*. Of these 79, a marked reaction was present in 22, who were accordingly selected for a detailed examination. In 3 of them the organism was recovered from both blood and urine, in 1 from the blood only, and in 6 from the urine only. All these men were up and about and in full work during the period of observation. Two were kept under observation and continued to pass large numbers of micrococci in the urine from June, 1905, until the end of 1906, and are probably still excreting them (1907).

Although the micrococci have only been directly observed in the fæces of man on one occasion, they probably also pass out of the body by way of the alimentary canal. Eyre found micrococci throughout the whole length of the intestine in artificially inoculated rabbits. Horrocks and Kennedy have also found them in the gall bladder of man.

A third way of leaving the body is by the milk, and this is by far the most important from the point of view of infection. Naturally, it is difficult to obtain evidence of this mode of excretion in patients, on account of the absence of lactation in patients who have Malta fever. During the summer of 1906, however, 3 women were examined and the micrococcus recovered from the milk of 2 of them.

Although these three modes of leaving the body are probably the most important, yet a fourth remains for discussion. The blood of Malta fever patients contains micrococci, not in large numbers as a rule it is true, but still in appreciable amount. Now, a mosquito takes in about four milligrams of blood at each feeding, and, therefore, it is quite possible for the mosquito to ingest this micrococcus with the blood. Horrocks and Kennedy did in fact isolate *M. melitensis* on four occasions from the blood contained in the stomach of mosquitoes caught in fever wards.

How Does the Micrococcus Enter the Body ?—The success of preventive measures probably hangs on finding the correct answer to this question. Does the virus enter by way of the alimentary canal, by the lungs, through mucous membranes, or through the skin ? In other words, is it conveyed from the sick to the healthy by means of food, water, milk, by the inhalation of dust, or is it injected through the skin by suctorial insects ?

In trying to frame preventive rules against an infectious disease it is evident that the important thing to strive for is the narrowing down of the paths of infection. In yellow fever, as long as it was believed that it could be spread by contact, infected clothes, food, water, etc., nothing could be done. The moment the mode of infection was narrowed down to a particular species of mosquito the problem of prevention was simple. In the same way with Malta fever: if it can be spread by contact, contamination of food or

[1] *Reports of the Mediterranean Fever Commission*, vol. iv, p. 8.

water, by the inhalation of dust, sewer air, etc., it will be impossible to do more than recommend the ordinary established rules of hygiene. But, on the other hand, if the mode of spread can be narrowed down to such a vehicle as milk or a mosquito, something rapid and dramatic in the way of prevention might be attempted.

By Contact.—Many experiments have been made on this point, as naturally, questions of segregation of the sick, evacuation and disinfection of infected barracks and rooms depend on this mode of infection. In 1904 two monkeys belonging to the Mediterranean Fever Commission took the fever naturally. They were both living close to affected monkeys, and it was supposed, and probably rightly so, that they had taken the disease from their neighbors. This was repeated as an experiment on several occasions with, as a rule, positive results. Experiments made in which the contact was limited, that is to say, in which infection by urine was excluded, never succeeded. It was therefore concluded that the monkeys probably took the disease by having their food contaminated with the urine of their neighbors; or it might possibly be by eating ectoparasites containing blood; and that, therefore, contact resolved itself into a feeding experiment.

As the chance of man having his food contaminated in this way is very remote, it is probable that very few cases of Malta fever arise in this manner.

At the same time, this mode of infection cannot be absolutely excluded, and the high incidence, according to Johnstone, among those who nurse Malta fever patients may possibly be due to insufficient care in the handling of the urine of the patients. But the fact that no case of Malta fever has ever been known to occur in England, at Netley or Haslar Hospitals, where thousands of patients with this fever have been treated, is proof that, in practice, contact as a factor in the causation may be almost put out of court.

By Contaminated Dust.—As the organism can retain vitality for a long time in a dry condition, it was thought probable that the infection might be conveyed from the sick to the healthy by means of dust. Dust contaminated with urine from Malta fever cases might be blown into the atmosphere and so be inhaled or swallowed. In order to put this to the test various experiments were made. At first, artificially contaminated dust was used. The dust was sterilized, then made wet with an emulsion of the organisms from agar cultures, and finally dried. Horrocks relates 2 experiments, in 1 of which this dust was blown about the cage, and in the other blown directly into the nose and throat. Both were successful. Shaw also describes 2 experiments of blowing contaminated dust about an air-tight box containing the monkeys, but both were unsuccessful. In 2 experiments by him in which the dust was blown into the nostrils, 1 remained negative, and 1 gave a positive result. Of 4 experiments in which he frequently dropped dust into the conjunctival sac, 2 were negative and 2 positive.

From these experiments it may be concluded that *artificially* contaminated dust may convey Malta fever to healthy animals. This is not proof, however, that this ever occurs naturally. Artificially contaminated dust contains myriads of the specific micrococci. Dust in nature can contain but few, seeing how sparse they are in the urine as a rule. The dust blowing about under natural conditions must rapidly dilute the micrococci to an extraordinary extent, so that we can only picture a micrococcus here and there in a great quantity of dust. The natural conditions can be more closely imitated if the dust is contaminated with Malta fever urine and not from a culture.

By Dust Artificially Contaminated with the Urine of Malta Fever Patients.—A urine containing micrococci was used to contaminate the dust. After drying, the infective dust was blown into the nostrils and added to the food of monkeys. Four experiments are reported by Horrocks, lasting from twelve days to two months, but in no case did infection occur. It is difficult to understand why this experiment did not succeed. The dust was infected by a urine containing exceptionally large numbers of the micrococci, and immediately dried. It was evidently added in fairly large quantities to the food, as three out of four animals suffered from severe vomiting and diarrhœa. Shaw also reports that he experimented on four monkeys in the same way, but did not succeed in conveying the infection in a single case. These experiments are much more severe than anything we can imagine occurring in nature, and tend to throw doubt on dust being an important factor in the spread of Malta fever.

By Dust Collected from Suspicious Places.—This is, of course, the crucial experiment as far as infection by dust is concerned. Judging from the non-success of the last series of experiments with urine-contaminated dust, it was little likely that this experiment would succeed. It was, however, necessary to make the attempt. Dust was collected from fever wards, from places where cases had occurred, from around urinals, etc., and blown about the cages and food of monkeys, or injected subcutaneously. Up to the present all these experiments have failed.

When one considers the numbers of ambulatory and convalescent patients who must frequently be excreting this organism in the urine, one is led to think that this must constitute a means of spreading the disease. At the same time there is no absolute proof that this is so; the micrococcus has never been recovered from urine-contaminated places, or from the dust of such places; nor has the disease been set up in any animal by artificial inoculation with material from such places. Theoretically, there seems to be danger from the scattering broadcast of such a virulent and resistant microbe, but it is possible that not a single case of infection occurs in this way. As sound practice, however, any sanitary measures which could be devised to prevent the fouling of the soil by infected urine would be advisable.

By Way of the Alimentary Canal.—It has been repeatedly demonstrated by experiment that a small quantity of a culture applied to a scratch, or injected under the skin, will give rise to Malta fever in man and monkeys. Also that dust or fluids containing the micrococci, if applied to the unbroken conjunctiva, nasal passages, pharynx, interior of the larynx and trachea of monkeys, will set up this fever.

This question of the micrococcus gaining entrance by way of the alimentary canal is important. It is most essential that it should be known without any shadow of doubt whether or not a man can take this fever by swallowing the micrococci in his food or drink. It would also be well to know if this mode of infection takes place readily and whether many micrococci are necessary or some particular state of the digestive organs. A careful study of the evidence must convince anyone that Malta fever can be conveyed to healthy animals by way of the alimentary canal. Many animal experiments were made by the commission to settle this point, with the result that it is abundantly proved that animals can be readily infected by contaminated food or drink. For example, a single drink of milk containing comparatively few micrococci almost certainly gave rise to the fever.

By Mosquitoes or Other Biting Insects.—All the various species of mosquitoes found in Malta, other biting flies, as Stomoxys, fleas, etc., were first fed on affected animals and then at various intervals of time on healthy monkeys. The results of numerous experiments go to show that although such a method of infection is not absolutely disproved, it can only be of very rare occurrence.

As the result of all these experiments it stands out fairly clearly that the *Micrococcus melitensis* is conveyed from the sick to the healthy by way of the alimentary canal and therefore by some infected food or drink. There is no reason to believe that contact, inhalation of infective dust, or biting insects, play any prominent role. Then, again, from a study of the epidemiology of the fever, no suspicion could be attached to the water supply or any particular foodstuff.

Infection by Means of Goats' Milk.—As part of an investigation of this sort, it is necessary to examine the various domestic animals to find out if any of them, through which man might be infected, are susceptible to the disease. The monkey was the only experimental animal known to take the disease naturally; but various others, such as the guinea-pig and rabbit, could be infected by various expedients.

Attention was directed to the goats, which are so numerous and so much a feature of every-day life in Malta, and which supply most of the milk used in the island. Healthy goats were injected subcutaneously with cultures of *Micrococcus melitensis*, and, although they showed no signs of fever or ill-health, an examination of their blood showed that the micrococci were living and growing. This remarkable and unlooked-for observation led to the examination of various herds of apparently healthy goats perambulating the streets, and supplying the inhabitants with milk, and the important discovery was made that about 50 per cent. were affected by the disease, and that 10 per cent. were actually excreting the micrococcus in their milk. Monkeys fed on milk from an affected goat, even for one day, almost invariably took the disease. At this time, curiously enough, an important experiment on the drinking of goats' milk by man occurred accidentally. This is the case of the S. S. "Joshua Nicholson." In 1905 this steamer shipped sixty-five goats at Malta for export to the United States of America. The milk was drunk by the captain and many of the crew, with the result that an epidemic of Malta fever broke out on board the vessel, almost everyone who drank the milk being infected. Even after the goats reached America and were placed in quarantine, a woman who drank some of their milk had the fever.

Here, at last, a mode of infection was discovered which explained many of the curious features in the epidemiology of Malta fever: The irregular seasonal prevalence and the number of cases during the winter months, when there are no mosquitoes and little dust. It is true there are more cases in summer, but this may be explained by the conditions being more favorable for the multiplication of the micrococcus, by more milk or cream being used for fruit, in ice-cream, etc., and by the lowering of health during the hot months. It would explain the large number of cases arising among patients in hospitals where milk is used largely. It would also explain the liability to attack of the officer being three times as great as the private soldier, since the former consumes much more milk than the latter. It would also explain the isolated epidemics which sometimes occur in institutions, or in messes, such

as that related by Johnstone, where a sergeants' mess was severely infected while the men living in the vicinity escaped.

Result of Preventive Measures Directed against the Use of Goat's Milk.—Preventive measures, as the result of the discovery of infection among the goats, were first begun in Malta in June, 1906. The result was very striking. In July, August and September, 1905, there had been 258 cases among the soldiers, whereas in the same months in 1906 the number fell to 26. It must also be mentioned that 1906 began badly, there being an average incidence of 31 per 1,000 for the first six months of 1906 against 27.6 per 1,000 for the years 1899 to 1905.

Another striking example of the benefit of this simple preventive measure is given in the case of the Naval Hospital, Malta. This is a fine modern building, situated in extensive grounds. In spite of these advantages it had been in bad repute, on account of the number of cases of Malta fever which occurred among the inmates. Almost every patient who remained for a few weeks in the hospital took the disease. The goats supplying the hospital with milk were examined and several found to be passing the micrococcus in their milk. The use of goats' milk was forbidden, and from that date not a single case of Malta fever has appeared in the hospital.

A still more striking proof is afforded in Gibraltar, where some years ago this fever was prevalent. Gradually it grew less and less and finally has quite disappeared. Horrocks, who investigated this point, found that Malta fever had disappeared from Gibraltar *pari passu* with the disappearance of Maltese goats.

Taking all these facts into consideration, there seems reasonable ground for the belief that nine-tenths of the cases of Malta fever which occur in Malta are due to infection by goats' milk, and for the hope that Malta fever will be driven out and 74,880 days of severe illness blotted out of the yearly medical reports of the army and navy. This, if brought about, will be a brilliant achievement in the annals of preventive medicine, and will once more demonstrate the value of experimental methods in the elucidation of the etiology of disease. It is too early to be quite dogmatic, but the prospect appears hopeful, and the result of next year's campaign against this fever will be awaited with some anxiety and much interest.

Age and Sex.—There are no statistics available at the present time to enable us to state whether age or sex has any bearing on the incidence. In former papers by the writer, the opinion was hazarded that any age is liable and that sex has no influence.

Length of Residence.—According to Johnstone,[1] the heaviest incidence is among soldiers during their first year's service in Malta, and the severity of incidence continues to decrease with length of residence.

Mode of Prevalence.—This is curious and must depend on some particular cause. The officers and their wives and families, living in large, well-ventilated, well-cared-for houses, suffer more frequently than the non-commissioned officers and men, living in crowded barrack rooms. The disease occurs over all the island. Water supply, sanitary arrangements, or their absence, do not seem to affect the incidence. Now that the discovery of the infection among the goats has been brought to light, this peculiarity in the mode of prevalence is explained.

[1] *Reports of the Mediterranean Fever Commission,* vol. ii, p. 33.

Months and Seasons.—Tables and curves have been constructed by Johnstone,[1] and others, showing the relation of Malta fever to temperature and rainfall. From these it is seen that there is a close correspondence between the temperature curve and the Malta fever curve. As Johnstone points out, the rise of the latter curve follows that of the former at an interval of about one month, which would be approximately sufficient to allow for incubation and notification if the incidence of the fever were directly dependent on the temperature of the air. The rainfall curve is, broadly speaking, the opposite of the temperature curve, but the relation of the fever to the rainfall does not seem to be as manifest as its connection with the temperature. It must be noted, however, that, although the number of cases which occurs during the wet winter months is much smaller than that which occurs in the summer months, yet the fever by no means dies out, but continues all the year round, there being, roughly, a third as many cases notified during February as in August. It is difficult to believe that this fever is mainly carried by means of dust, as has been advanced, if one-third as many cases occur in the depth of winter, in the rainy season, as occur during the rainless months of July and August.

Incubation Period.—It is impossible to state exactly what the period of incubation is. Johnstone, who has gone into this subject as fully as possible, provisionally states that the available data tend to suggest that the incubation period is about fourteen days. One case is reported by Bassett-Smith with an incubation period of two months, but it stands alone, and there is some evidence that cases have occurred in as short a time as six days after arrival in Malta. The subcutaneous inoculation of monkeys gives an incubation period of about five days, whereas if the disease is given by ingestion the inoculation period appears to be lengthened to about fifteen days.

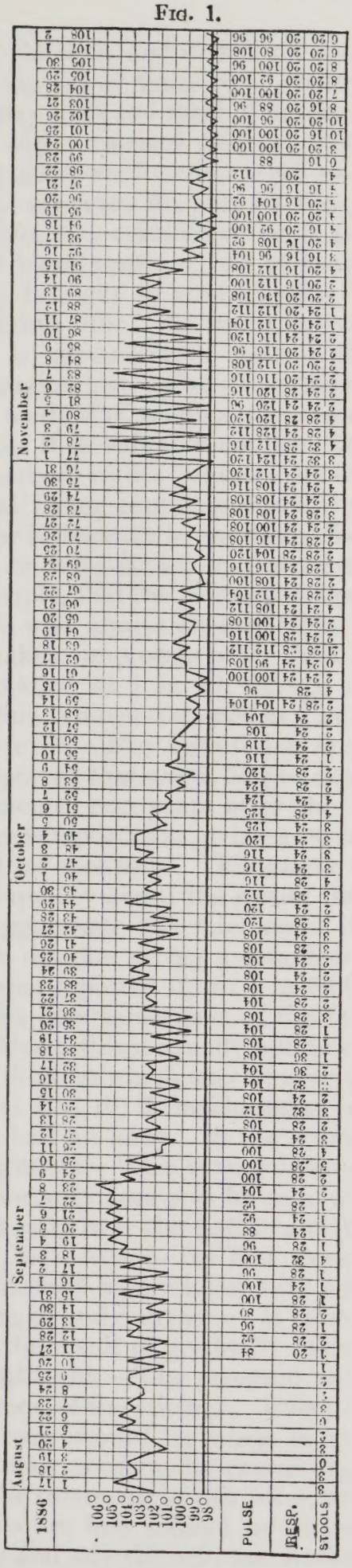
Immunity from Second Attack.—Although there is some diversity of opinion the writer's experience suggests that one attack of this fever does practically confer immunity. Lately, several monkeys which had recovered from the disease were reinoculated with a virulent culture and showed no reaction.

Special Pathology.—The anatomical changes are those due to high temperature and the circulation of toxins in the blood, and need not be described in detail. There is absolutely no specific inflammation of Peyer's patches, or other glands of the intestine. The spleen is always enlarged, averaging 20 ounces in weight. The mesenteric glands are only moderately enlarged, showing a marked contrast to typhoid fever. The lungs are always congested at the bases, but there is less liability to pneumonic consolidation than in typhoid fever.

Symptoms.—There is no great necessity to enter into the symptomatology at great length, as the symptoms are those commonly met with in other fevers, such as typhoid fever. There are, however, a few points which should be noted. For example, constipation is a marked symptom in Malta fever; in 65 cases, 48 are noted as being constipated throughout, whereas only 17 had diarrhœa at any time during the illness. The temperature curve must also be noted. On looking over a series of charts, the striking features are the extreme irregularity and the great tendency to relapses. The following chart may be taken as typical of a fairly severe attack of Malta fever, and from it can be judged the length and serious nature of the disease.

[1] *Report of the Mediterranean Fever Commission,* vol. ii, p. 35.

FIG. 1.



Duration of the Fever.—The average stay of soldiers in hospital is ninety days, but this does not represent the true average, as many of these men are invalided to England. Bassett-Smith gives the average duration in 50 cases at one hundred and twenty days. The length of this fever varies in different individuals between wide limits; while some return to duty within twenty or thirty days, on the other hand the writer has seen a case which lasted for more than three years.

Another important symptom is the pain and swelling of the joints. This complication occurs in nearly half the cases, and is very characteristic of the disease. Neuritis and orchitis come under the same category, and are fairly frequent. The orchitis is painful while it lasts, but usually passes away in a few days without leaving any bad effects.

Sequelæ.—There is little to be noted under this heading. Although considerable pain and inconvenience are caused by the swelling of, and effusion into, the joints, the arthritis usually clears completely and does no permanent damage. Neuritis is frequent in various nerves, and naturally tends to cause, in a few cases, prolonged anæsthesia, paresis, or even paralysis, of various regions and groups of muscles. In time these return to normal, and one can, as a rule, safely assure the patient of a return to complete health sooner or later.

Mortality.—The disease is not a very fatal one, 3 per cent. being the case mortality in the army during a period of seven years.

Diagnosis.—This is most important clinically in the distinction from typhoid fever, from which it differs chiefly in the longer duration, in the absence of rose spots, in constipation being the rule, in the frequent occurrence of painful arthritic or neuralgic symptoms, and, finally, in the much smaller rate of mortality. The surest method of diagnosis is the finding of the *Micrococcus melitensis* in the blood, *intra vitam*, or growing it from the spleen *postmortem*.

Shaw examined the blood of Malta fever patients on 51 occasions and found the micrococcus 30 times. His method was to draw off a few cubic centimeters of blood from a

vein of the arm and distribute it over several broth tubes. Zammit also was successful 27 times in 50 observations. He introduced a method which does away with the need of entering a vein. The finger or lobe of the ear is thoroughly cleaned and the dry skin is punctured with a needle. A sterile cotton-wool pad is used to remove the first drop of blood and an assistant squeezes the part for the next drop. A number of sterilized capillary tubes, one centimeter long, are ready in a test-tube. As soon as the drop of blood appears, one of these capillary tubes, held by sterilized forceps, is brought in contact with it, and when full, immediately dropped into a broth tube. Six tubes are usually filled.

If it is impossible to make a diagnosis in this way there remains the agglutination test. The writer must say that he has not as much confidence in this method of diagnosis as many profess to have. As one factor in the diagnosis it is valuable enough, but to trust to it alone is dangerous. It is a method which requires some experience to get good results. The personal factor comes in strongly; what is positive sedimentation to one observer is negative to another. Every examination of blood by this method should be safeguarded by control experiments. It must be borne in mind, for example, that the *Micrococcus melitensis* will give a positive agglutination reaction with almost all specimens of serum in dilutions of 1 in 2 and that blood taken from cases other than Malta fever will sometimes show signs of agglutination at 1 in 10, though this is the exception. A complete sedimentation is never obtained at 1 in 20 unless the blood is from a patient with Malta fever. The agglutinins may persist in the blood for long periods. It is reported that about 50 per cent. of patients will show the agglutination phenomenon two years after the illness in dilutions of 1 in 10, and one instance is reported as giving a positive reaction in a dilution of 1 in 20, seven years after recovery. This source of error must therefore be kept in mind.

One quality about the serum from patients with Malta fever is that if it does agglutinate the micrococci it does this in no uncertain way. The average dilution giving a complete reaction is given as 1 in 500, and cases have been reported up to 1 in 6,000. In regard to the time which elapses from the commencement of the fever to the appearance of the agglutinins in the blood, this is usually put down as occurring on the fifth day. As to the lowest dilution which may be accepted as proof of Malta fever, some workers put it at 1 in 10, if the clumping is well marked and takes place at once or within half an hour. In the writer's opinion 1 in 20 is a safer dilution.

Prognosis.—This is very favorable as regards life and ultimate recovery. The mortality seems to be somewhere between 2 and 3 per cent. If the patient tides over the first two or three weeks, he usually recovers. Death occurs, as a rule, in the first week or two of the disease, and is preceded by continued high temperature with a tendency to hyperpyrexia, delirium, dry tongue and diarrhœa. It is true that a patient sometimes dies at a later stage, the result of gradually increasing debility, but this is rare.

Treatment.—The essential points in prophylaxis are evident from the discussion of the etiology. Infection being frequent by the alimentary tract, every care should be taken to exclude all articles of food from the diet which may contain the causal organism.

In the treatment of this fever, there is no specific drug and the majority of patients are best treated by leaving out medicines altogether. Quinine is useless and salicylic acid and its derivatives equally so. The symptoms must

be treated on ordinary principles as they arise. The tendency to hyperpyrexia in severe attacks is one of the most important and dangerous of the symptoms and one of the most difficult to treat. It is doubtful if any real good is got from medicinal antipyretics, but careful watching and timely recourse to the cold bath may sometimes save life. Hydrotherapy is probably the most useful measure, sponges or baths being given. Sleeplessness, headache, arthritis and orchitis must be treated on ordinary principles.